ANDA 74-889

OCT 31 1997

Apothecon, Inc.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

Dear Dr. Jump:

This is in reference to your abbreviated new drug application dated April 18, 1996, and found acceptable for filing on May 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated November 6, 1996, February 4, June 6, September 9 and September 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules 200 mg to be bioequivalent and therefore, therapeutically equivalent to those of the listed drug (Zovirax® Capsules 200 mg of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

10/30/97

Douglas L. Spdrn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture.
Dispense in a tight, light-resistant container.

Exp. Date
Control No. OCT 31 19

100 capsules NDC 59772-4168-2

ACYCLOVIR CAPSULES

Each capsule contains
200 mg

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

APPROVED

For indications, dosage, precautions, etc., see accompanying package insert.
Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland, CH-4800 for
APOTHECON® A Bristol-Myers Squibb Company,
Princeton, NJ 08540 USA
416821-01

3 59772 41682 4

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture.
Dispense in a tight, light-resistant container.

Exp. Date
Control No. 31

500 capsules NDC 59772-4168-3

ACYCLOVIR CAPSULES

Each capsule contains
200 mg

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

For indications, dosage, precautions, etc., see accompanying package insert.
Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland, CH-4800 for
APOTHECON® A Bristol-Myers Squibb Company,
Princeton, NJ 08540 USA
416830-01

3 59772 41683 1

Exp. Date
Control No.

100 capsules NDC 59772-4168-1
(10 blisterpacks of 10 capsules each)

UNIT DOSE PACK
ACYCLOVIR CAPSULES
Each capsule contains
200 mg

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture. Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided.
For indications, dosage, precautions, etc., see accompanying package insert.

Manufactured by
Siegfried Pharma AG/LTD,
Zofingen, Switzerland,
CH-4800 for

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA
416810-01

3 59772 41681 7

NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Apothecon® Princeton, NJ 08540 USA
NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA

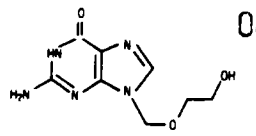
APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

APPROVED
OCT 31 1997

ACYCLOVIR CAPSULES & TABLETS

DESCRIPTION

Acyclovir is an antiviral drug. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxy-ethoxy)methyl]-6*H*-purin-6-one; it has the following structural formula:



$C_8H_{11}N_5O_3$

Acyclovir is a white to off-white crystalline powder with a molecular weight of 225.21 and a maximum solubility in water of 2.5 mg/mL at 37°C. The pKa's of acyclovir are 2.27 and 9.25.

Each capsule for oral administration contains 200 mg of acyclovir. In addition, each capsule contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and sodium starch glycolate. The capsule shell consists of gelatin, FD&C Blue No. 2 and titanium dioxide and is printed with iron oxide black ink.

Each tablet for oral administration contains 400 mg or 800 mg of acyclovir. In addition, each tablets contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide anhydrous, and sodium starch glycolate.

VIROLOGY

Mechanism of Antiviral Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by viral TK.

Antiviral Activities

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance

Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanism as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response to therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma Protein binding	9% to 33%
Plasma elimination half-life	2.5 to 3.3 hr
Average oral bioavailability	10% to 20%*

*Bioavailability decreases with increasing dose.

In one multiple-dose, cross-over study in healthy subjects (n=23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in Table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

Parameter	200 mg	400 mg	800 mg
C^{SS}_{max}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C^{SS}_{trough}	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir capsules and tablets may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy)methyl]guanine.

Special Populations

Adults with Impaired Renal Function

The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Pediatrics

In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2 in pediatric patients ages 7 months to 7 years was 2.6 hours (range 1.59 to 3.74 hours).

Drug Interactions

Co-administration of probenecid with intravenous acyclovir has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

Clinical Trials

Initial Genital Herpes

Double-blind, placebo-controlled studies have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection and duration of lesion healing. The duration of pain and new lesion formation was decreased in some patient groups.

Recurrent Genital Herpes

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 10 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of patients who received acyclovir 400 mg twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the patients showed that 71% to 87% were recurrence-free in each quarter.

Herpes Zoster Infections

In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double-blind, placebo-controlled study, acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).

Treatment was begun within 72 hours of rash onset and was most effective if started within the first 48 hours. Adults greater than 50 years of age showed greater benefit.

Chickenpox

Three randomized, double-blind, placebo-controlled trials were conducted in 993 pediatric patients ages 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, acyclovir was administered at 20 mg/kg four times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered four times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing, reduced the maximum number of lesions, reduced the median number of vesicles, decreased the median number of residual lesions on day 28, and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with acyclovir did not affect varicella-zoster virus-specific humoral or cellular immune responses at 1 month or 1 year following treatment.

INDICATIONS AND USAGE

Herpes Zoster Infections

Acyclovir is indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes

Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

Chickenpox

Acyclovir is indicated for the treatment of chickenpox (varicella).

CONTRAINDICATIONS

Acyclovir capsules and tablets are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS

Acyclovir capsules and tablets are intended for oral ingestion only.

PRECAUTIONS

Dosage adjustment is recommended when administering acyclovir to patients with renal impairment (see **DOSAGE AND ADMINISTRATION**). Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Information for Patients

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Herpes Zoster

There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections

Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox

Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

Drug Interactions

See **CLINICAL PHARMACOLOGY: Pharmacokinetics.**

Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Maximum plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two *in vitro* cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in five *in vitro* cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two *in vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No mutagenic activity was demonstrated in another, possibly less sensitive, *in vitro* cell transformation assay.

Acyclovir was clastogenic in Chinese hamsters at 380 to 760 times human levels. In rats, acyclovir produced a non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At higher doses (50 mg/kg/day, s.c.) in the rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, i.v. for 1 month (21 to 41 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (six to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B

Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiological registry of acyclovir use during pregnancy has been ongoing since 1984. As of June 1996, outcomes of live births have been documented in 494 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when it is indicated.

Geriatric Use

Clinical studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

Pediatric Use

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex

Short-Term Administration

The most frequent adverse events reported during clinical trials of treatment of genital herpes with acyclovir 200 mg administered orally 5 times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration

The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

Herpes Zoster

The most frequent adverse event reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

Chickenpox

The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral acyclovir at doses of 10 to 20 mg/kg four times daily for 5 to 7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%). The 498 patients receiving placebo reported diarrhea (2.2%).

Observed During Clinical Practice

Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Acute Treatment of Herpes Zoster

800 mg every 4 hours orally, 5 times daily for 7 to 10 days.

Genital Herpes

Treatment of Initial Genital Herpes: 200 mg every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg 2 times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir.

Intermittent Therapy: 200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of Chickenpox

Children (2 years of age and older): 20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg 4 times daily for 5 days.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs or symptoms.

Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

Patients With Acute or Chronic Renal Impairment:

In patients with renal impairment, the dose of acyclovir capsules or tablets should be modified as shown in Table 3.

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.

Bioequivalence of Dosage Forms

Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and one acyclovir 800 mg tablet was shown to be bioequivalent to 4 acyclovir 200 mg capsules (n=24).

HOW SUPPLIED

Acyclovir Tablets and Capsules are available as:

Acyclovir Tablets			
400 mg	Unit Dose Packs of 100	NDC 59772-4165-1	Each 12 mm, round, beveled-edge, unscored tablet is white, off-white and debossed with AP 4165.
	bottles of 100	NDC 59772-4165-2	
800 mg	Unit Dose Packs of 100	NDC 59772-4166-1	Each 21.5 mm x 9.5 mm capsule-shaped, beveled-edge unscored tablet is white, off-white and debossed with AP 4166.
	bottles of 100	NDC 59772-4166-2	
	bottles of 500	NDC 59772-4166-3	
Acyclovir Capsules			
200 mg	Unit Dose Packs of 100	NDC 59772-4168-1	Each size 1 capsule with blue cap and white body is printed in black ink with AP 4168.
	bottles of 100	NDC 59772-4168-2	
	bottles of 500	NDC 59772-4168-3	

Storage

Store at 15° to 25°C (59° to 77°F) and protect from light and moisture.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland CH-4800 for

ApotheconⓇ

A Bristol-Myers Squibb Company

Princeton, NJ 08540 USA

Acy74891, issued September 1997

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-889

3. NAME AND ADDRESS OF APPLICANT

Apothecon, Inc.
A Bristol-Myers Squibb Co.
P.O. Box 4500
Princeton, NJ 08543-4500

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, a New Chemical Entity exclusivity period expired on March 29, 1992, an indication of acute treatment of varicella zoster virus expired on April 26, 1993 and the indication of varicella infections (chickenpox) expired on February 26, 1995. The applicant will not claim an indication of varicella infections (chickenpox) until the expiration of this exclusivity period (February 26, 1995). Furthermore, the product will not be made available for sale until the expiration of U.S. Patent No. 4,199,574 on April 22, 1997.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

4-18-96: Original
5-30-96: Amendment for receipt of acceptable for filing
2-4-97: Amendment
9-9-97: Amendment

FDA:
5-15-96: refuse to file
6-13-96: Acknowledgement
1-14-97: 1st NA letter
8-29-97: 2nd NA letter

10. PHARMACOLOGICAL CATEGORY

Antiviral

11. Rx or OTC

℞

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Capsule

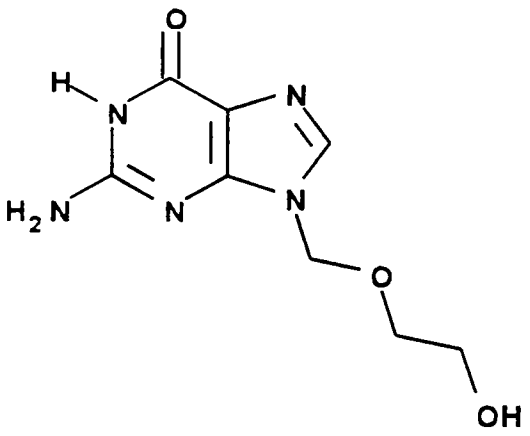
14. POTENCY

200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

$C_8H_{11}N_5O_3$; M.W. = 225.21
CAS [59277-89-3]



1. 9-[(2-Hydroxyethoxy)methyl]guanine.

2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. LD_{50} in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Q: 1.

A: OK (see response item 1 and Appendix 1 of the 9-9-97 amendment).

Q: 2.

A: OK (see response item 2 of the 9-9-97 amendment).

Q: 3.

A: OK (see response item 3 and Appendix 2 of the 9-9-97 amendment).

Q: 4.

A: OK (see response item 2 and Appendix 3 of the 9-9-97 amendment).

Q: 5. Your finished product release/stability specifications should be revised to incorporate the FDA recommended dissolution method and specification:

Not less than (Q) of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

A: OK (see response items 4 and Appendix 2 & 4 of the 9-9-97 amendment).

Q: 6. Formulation (complete composition of the drug product) has historically been requested to be included on stability reports. Other information such as description of the capsule and color of the imprinting ink should also be included.

A: OK (see response items 6 of the 9-9-97 amendment).

Q: 7.

A: OK (see response items 7 and Appendix 3 of the 9-9-97 amendment).

Q: 8. We note that moisture test was listed in the stability protocol on page 45c of the February 4, 1997 amendment. Please provide limits.

A: OK (see response items 8 and Appendix 2 & 4 of the 9-9-97 amendment).

Q: 9. Submit the updated release specifications of the finished product, stability protocol and stability data to incorporate the above comments.

A: OK (see response items 9 and Appendix 2 & 4 of the 9-9-97 amendment).

Status:

a. **EER:** Satisfactory

b. **MV** (method validation): Pending

Drug dosage form is not compendial. Method validation for the finished product was sent to Philadelphia District Laboratory on June 24, 1997 and found acceptable on 10-17-97.

c. **Bio-Review:** Satisfactory

Satisfactory per H. Nguyen reviewed on 10/2/97.

d. **Labeling review: Satisfactory**

per A. Vezza reviewed on 9-29-97.

e. **DMFs: Satisfactory**

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 10-3-97

D N

ANDA 74-889

OCT - 9 1997

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules, 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

   Not less than ' of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT - 2 1997 9 N

Acyclovir Capsules
AADA #74-889: 200 mg
Reviewer: Hoainhon Nguyen
WP #74889d.697

Apothecon
Princeton, NJ
Submission Date:
June 6, 1997

Review of Dissolution Data

The firm has submitted the current amendment in response to the Division of Bioequivalence's deficiency comments in the letter issued April 30, 1997. The division recommended the current FDA interim dissolution procedure and specifications be used for the test product until USP dissolution procedure and specifications become official. Since the firm had conducted the dissolution testing on the test product using the interim method on only 6 units instead of 12, the data were considered insufficient and additional testing was requested.

In this amendment, the requested additional data were provided. Since the data for the test product bio lot did not meet the USP Acceptance Criteria - S_1 Stage, the firm also included data of additional testing of 18 units for the same lot. The first 12 additional capsules complied with USP S_3 Stage. The dissolution results are in the review attachment.

Comment and Recommendation:

1. The in-vitro dissolution testing conducted by Apothecon on its Acyclovir Capsules, USP, 200 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXIII apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

2. As recommended in the previous review of the submission dated April 18, 1996, the single-dose, fasting and non-fasting bioequivalence studies conducted by Apothecon on the test product, Acyclovir Capsules, 200 mg, lot # 9509B004, comparing it with the reference product, Zovirax^{R} Capsules, 200 mg, lot # 5M1295, have been found **acceptable** by the Division of Bioequivalence. The studies demonstrate that the test product is bioequivalent to the reference product under fasting and non-fasting conditions.

The firm should be informed of the Recommendation.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 9/12/97

Concur: _____ Date: 10/2/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: AADA #74-889(original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/09-09-97/WP#74889d.697
Attachment: 2 pages

NDA #74559 d. 6/97 Attachment (Page 1 of 2)

Test Samples

Zovirax® Capsules 200 mg, Lot 4X1885 (Expiration Date 10/97)
Distributor: Burroughs Wellcome Co.
Package: Plastic Bottle, White (100 units)

Apothecon Acyclovir Capsules 200 mg, Batch 9509B004

Dissolution Data

Conditions: USP 23 Apparatus I (basket), 100 RPM, 900 mL deaerated water

ZOVIRAX® CAPSULES 200 MG, LOT 4X1885

Capsule No.	0 Minutes	5 Minutes	10 Minutes	20 Minutes	30 Minutes	45 Minutes	60 Minutes
7							
8							
9							
10							
11							
12							
Mean	-	29.1%	63.3%	80.1%	88.4%	97.1%	98.8%
SD	-	10.8%	19.9%	10.9%	7.0%	1.6%	1.7%

Apothecon ACYCLOVIR CAPSULES 200 MG, BATCH 9509B004

Capsule No.	0 Minutes	5 Minutes	10 Minutes	20 Minutes	30 Minutes	45 Minutes	60 Minutes
7							
8							
9							
10							
11							
12							
Mean	-	28.1%	65.5%	89.5%	93.0%	95.6%	96.8%
SD	-	5.3%	18.3%	15.9%	12.7%	8.8%	6.8%

Test Samples

Apothecon Acyclovir Capsules 200 mg, Batch 9509B004

Dissolution Data

Conditions: USP 23 Apparatus I (basket), 100 RPM, 900 mL deaerated water

Apothecon ACYCLOVIR CAPSULES 200 MG, BATCH 9509B004

Capsule No.	30 Minutes
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	

ANDA 74-889

APR 30 1997

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

Dear Sir:

Reference is made to the Abbreviated New Drug Application amendment submitted on November 6, 1996, for Acyclovir Capsules 200 mg.

The Office of Generic Drugs (OGD) has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. OGD acknowledges that the reference product does not meet the specification of "NLT dissolved in 30 minutes", as shown in the above amendment.

2. The FDA recommended **interim** dissolution requirements should be conducted using the following dissolution methodology and specifications:

   Apparatus: USP 23 Apparatus I (basket)
   Speed: 100 rpm
   Medium: Deaerated water
   Volume: 900 mL
   Specifications: "Q": NLT in 30 minutes.

3. The dissolution data as submitted in this amendment follow the correct procedure. However, only 6 units were used instead of 12 units as required by the Agency. **Therefore, the data is insufficient and additional testing of the same lots for 6 more units is required.**

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

^

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 22 1997

Acyclovir Capsules
AADA #74-889: 200 mg
Reviewer: Hoainhon Nguyen
WP #74889a.n96

Apothecon
Princeton, NJ
Submission Date:
November 6, 1996

Review of an Amendment: Changes in Dissolution Specifications

The firm has submitted the current amendment in response to the Division of Bioequivalence's following deficiency comment included in the letter issued October 15, 1996:

"The dissolution testing for the test and reference products is not acceptable. The dissolution medium should be water instead of 0.1N H Cl, and the basket speed should be 100 rpm instead of 50 rpm. The current FDA-recommended dissolution specification is NLT of LC dissolved in 30 minutes."

The firm questioned the above FDA-recommended dissolution procedure and specifications because:

(i) The reference product fails to meet the specifications.

(ii) The FDA proposed specifications differ significantly from the proposed USP method of (Q) in 45 minutes (Pharmacopeia Forum 22, No. 4, p. 2487).

(iii) The 0.1 N HCl as dissolution medium simulates better the stomach environment than water.

Comments and Recommendations:

1. The Division of Bioequivalence acknowledges that the reference product does not meet the specification of "NLT dissolved in 30 minutes", as Apothecon's data showed in this amendment.

2. The FDA-recommended dissolution procedure and specification are being used as **the interim requirements** until official USP dissolution procedure and specification for the drug product are published. The USP dissolution requirements then will be considered the final regulatory specification. The firm therefore should be advised to follow the FDA-recommended method and specifications for the interim period.

3. The dissolution data as submitted in this amendment follow the correct procedure. However, the firm only used 6 units instead of 12 units as required by the agency. **The data are,therefore, insufficient and additional testing of the same lots for 6 more units is required.**

The firm should be informed of the division comments and recommendations.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 4/22/97

Concur: _____ Date: 4/22/97
~~for~~Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: AADA #74-889(original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/03-20-97/WP#74889a.n96/Revised 04-21-97
Attachment: 1 page

WP # 74889a.n 96 Attachment I

Dissolution data:

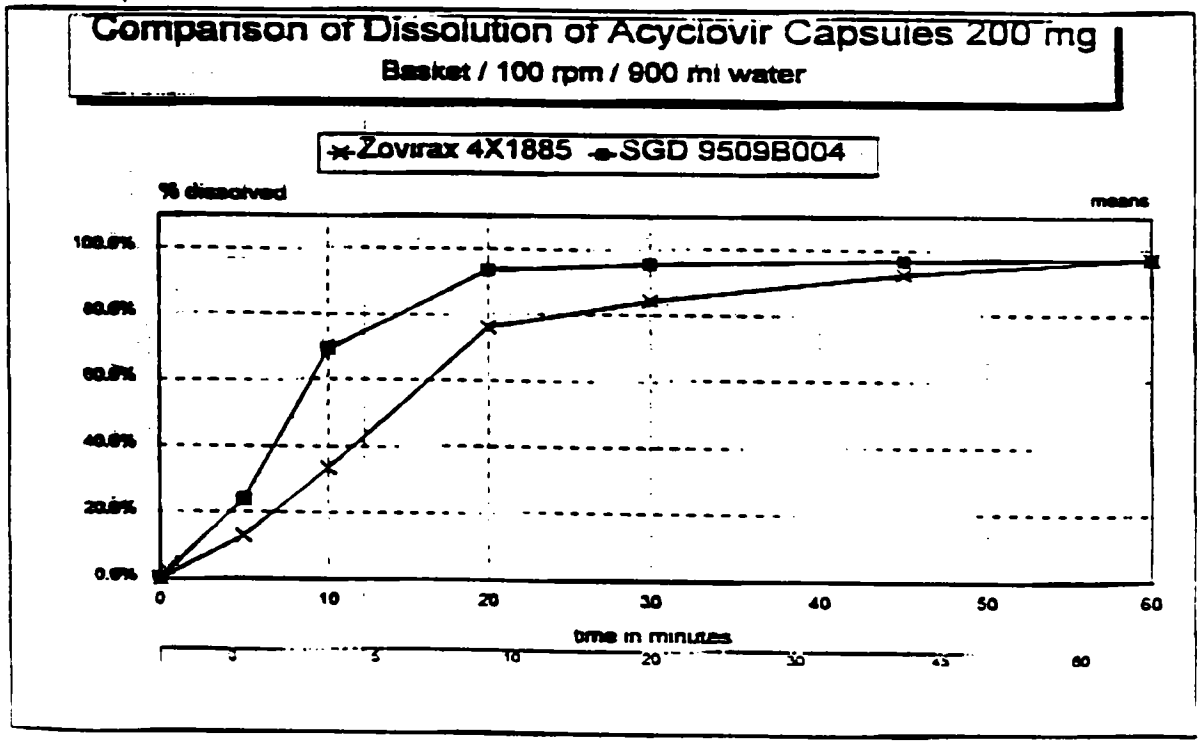
ZOVIRAX CAPSULES 200 MG, LOT 4X1885

	time in minutes						
	0	5	10	20	30	45	60
capsule 1	0						
capsule 2	0						
capsule 3	0						
capsule 4	0						
capsule 5	0						
capsule 6	0						
mean	0	13.1%	33.5%	76.1%	84.3%	92.5%	97.2%
SD	0	10.7%	8.9%	10.6%	6.7%	2.6%	1.0%

ACYCLOVIR CAPSULES 200 MG, BATCH 9509B004

	time in minutes						
	0	5	10	20	30	45	60
capsule 1	0						
capsule 2	0						
capsule 3	0						
capsule 4	0						
capsule 5	0						
capsule 6	0						
mean	0	24.1%	69.2%	93.5%	95.4%	96.7%	97.0%
SD	0	8.4%	4.4%	3.1%	2.5%	2.5%	2.3%

Dissolutionprofiles



ANDA 74-889

Apothecon, Inc.
A Bristol-Myers Squibb Co.,
Attention: Walter G. Jump, Pharm.D.
P.O. BOX 4500
Princeton NJ 08543-4500

OCT 15 1996

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on April 18, 1996, and was acceptable for filing on May 31, 1996, for Acyclovir Capsules, 200 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

> The dissolution testing for the test and reference products is not acceptable. The dissolution medium should be **water** instead of 0.1N HCl, and the basket speed should be **100 rpm** instead of 50 rpm. The current FDA-recommended dissolution specification is NLT of label claim dissolved in 30 minutes.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 26 1996

Acyclovir Capsules, 200 mg
ANDA # 74-889
Reviewer: Hoainhon Nguyen
WP # 74889s.496

Apothecon Inc.
Princeton, NJ
Submission Date:
April 18, 1996

Review of Bioequivalence Studies and Dissolution Data

I. Background:

Acyclovir is a synthetic purine nucleoside analog derived from guanine, used in the treatment of initial episodes, the management of recurrent episodes of genital herpes in certain patients and the acute treatment of herpes zoster (shingles) and chickenpox (varicella). The inhibitory activity of acyclovir for herpes simplex types 1(HSV-1) and 2(HSV-2), varicella-zoster virus(VZV) and Epstein-Barr virus(EBV) is highly selective. The enzyme thymidine kinase(TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV and EBV converts acyclovir into acyclovir monophosphate which is further converted into diphosphate and triphosphate by a number of cellular enzymes. Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. A maximum solubility of acyclovir in water is 2.5 mg/ml at 37°C. Dosage regimen for treatment of initial genital herpes is 200 mg every 4 hours.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated 15-30%. Reported values for CMAX and TMAX in healthy subjects after a 200 mg capsule were 0.3 ± 0.1 mg/l and 1.5-2.5 hours, respectively. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg in a study with steady-state peak and trough concentrations of acyclovir being 0.83 and 0.46 mcg/ml, 1.21 and 0.63 mcg/ml, and 1.61 and 0.83 mcg/ml for the 200, 400, and 800 mg dosage regimens, respectively.

Following oral administration, the mean half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. Acyclovir is predominantly eliminated by glomerular filtration and tubular secretion, with

approximately 45-79% of a dose recovered unchanged in the urine and about 15% as an inactive metabolite, 9-carboxymethoxymethyl-guanine. Acyclovir may decrease the renal clearance of other drugs, such as methotrexate, that are eliminated by active tubular secretion.

The influence of food on the absorption of acyclovir was not apparent.

Adverse effects associated with acyclovir include nausea and/or vomiting, diarrhea, dizziness, anorexia, fatigue, edema, skin rash, and headache.

Acyclovir is available commercially as Zovirax^{R} 200 mg capsules, 800 and 400 mg tablets, and oral suspension 200 mg/5 ml, manufactured by Burroughs-Wellcome.

The firm has submitted one fasting and one non-fasting, single-dose bioequivalence study comparing its Acyclovir Capsules, 200 mg, with Burroughs-Wellcome's Zovirax^{R} capsules, 200 mg. Comparative dissolution data for the test and reference products were also submitted.

II. Bioequivalence Studies:

A. Fasting Study: Study No. 9517202B

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Apothecon's acyclovir capsules, 200 mg, and Burroughs-Wellcome's Zovirax^{R} capsules, 200 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at between December 2, 1995 and December 10, 1995. The principal investigator was Plasma samples were assayed by under the supervision of between December 18, 1995 and January 12, 1996.

Demographics:

Thirty-eight normal, healthy, male volunteers between 19-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 133-194 lbs and 67-75 in., respectively. There were 21 caucasians, 16 blacks and 1 hispanic.

Inclusion criteria:

Subjects especially did not have any history of: chronic infectious disease, heart disease, pulmonary obstructive disease, hepatic or renal disease, bronchial asthma, or hypertension, gastrointestinal disease or malabsorption within the last year, psychiatric disorders, allergy and/or sensitivity to acyclovir, use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days prior to initial study dosing, or drug or alcohol addiction.

Restrictions:

They were free of all prescription medications at least 14 days and any over-the-counter 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed for 48 hours prior to initial study dosing until their release from confinement in each period. The subjects fasted for approximately 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was approximately 12 hours pre-dose to 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 400 mg dose (2x200 mg capsules) of either the test product or reference product taken orally with 240 ml of water.

Test Product: Apothecon's Acyclovir Capsules, 200 mg, lot # 9509B004 (Batch size of units, potency of 100.5%).

Reference product: Burroughs-Wellcome's Zovirax^{R} Capsules, 200 mg, lot # 5M1295 (Potency of 97.0%).

Blood samples were collected predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 19 and 24 hours following drug administration. Blood samples were heparinized centrifuged and the plasma was separated and immediately stored at -20°C until shipping to the analytical laboratory.

Assay Methodology:

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Thirty-seven of thirty-eight enrolled volunteers completed the clinical portion of the study. Subject # 28 was withdrawn from the study because of positive drug screen. The statistical analysis was performed using 37 data sets.

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T) and lnCMAX. There was a significant difference between treatments for lnAUC(0-Infinity)(p=0.0270). The results are summarized in the tables below:

Table I

Acyclovir Comparative Pharmacokinetic Parameters

Dose = 400 mg; n = 37

Parameters	Apothecon's Mean (CV)	Zovirax® Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) mcg.hr/ml	2.759*	2.529*	[0.98;1.22]	1.09
AUC (0-Inf) mcg.hr/ml	3.114*	2.754*	[1.03;1.24]	1.13
CMAX(mcg/ml)	0.6168*	0.5738*	[0.94;1.22]	1.08
TMAX (hrs)	1.77(39)	1.59(42)		
KEL (1/hrs)	0.209(27)	0.202(26)		
T1/2 (hrs)	3.74(48)	3.67(27)		

*Geometric LS Means

Table II

Comparative Mean Plasma Levels of Acyclovir

mcg/ml(CV)

Dose = 400 mg; n = 37

Hour	Apothecon's	Zovirax[R]
0	0	
0.25	0.006(348)	0.002(608)
0.5	0.142(67)	0.181(76)
1.0	0.498(41)	0.476(50)
1.50	0.604(46)	0.511(44)
2.0	0.586(44)	0.520(46)
2.5	0.554(45)	0.489(45)
3.0	0.510(46)	0.431(47)
4.0	0.371(49)	0.353(56)
5.0	0.282(47)	0.261(50)
6.0	0.216(46)	0.201(46)
8.0	0.135(42)	0.124(41)
10.0	0.081(53)	0.076(54)
12.0	0.042(93)	0.040(97)
15.0	0.012(194)	0.012(194)
19.0	0	0
24.0	0	0
AUC(0-T)mcg.hr/ml	3.027(43)	2.761(42)
AUC(0-Inf)mcg.hr/ml	3.382(38)	3.096(39)
CMAX	0.672(42)	0.624(42)

Adverse Effects:

None of the adverse reactions reported was serious. There were five and three subjects who reported adverse effects during the treatment of the test and reference products, respectively. The reactions judged probably or possibly related to the treatments were headache, tiredness, nausea and dizziness.

B. Non-Fasting Study: Study No. 9517203B

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Apothecon's acyclovir capsules, 200 mg, and Burroughs-Wellcome's Zovirax^{R} capsules, 200 mg, in a fasting/non-fasting single dose, three-treatment, three-period crossover study design.

Study Investigators and Facilities:

The study was conducted at between November 11. 1995 and November 26, 1995. The principal investigator was Plasma samples were assayed by under the supervision of , between December 7, 1995 and December 18, 1995.

Demographics:

Twenty-four normal, healthy, male volunteers between 18-48 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 133-187 lbs and 66-73 in., respectively. There were 12 caucasians and 12 blacks.

Inclusion criteria:

Same as in the Fasting Study Protocol above.

Restrictions:

They were free of all prescription medications at least 14 days and any over-the-counter 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were

allowed for 48 hours prior to initial study dosing until their release from confinement in each period. The subjects fasted for approximately 10 hours prior to and 4 hours after each drug administration during the fasting leg of the study. During the non-fasting legs, they were served a standardized breakfast at 0.33 hours prior to dosing following an overnight 10-hour fast. The washout duration between the phases was one week. Duration of confinement was approximately 12 hours pre-dose to 24 hours post-dose.

Treatments and Sampling:

The three treatments consisted of a single 400 mg dose (2x200 mg capsules) of either the test product or reference product taken orally with 240 ml of water.

Test Product: Apothecon's Acyclovir Capsules, 200 mg, lot # 9509B004 (Batch size of units, potency of 100.5%), given under fasting conditions (**Treatment A**), or under non-fasting conditions (**Treatment B**).

Reference product: Burroughs-Wellcome's Zovirax^{R} Capsules, 200 mg, lot # 5M1295 (Potency of 97.0%) given under non-fasting conditions (**Treatment C**).

Blood samples were collected predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 19 and 24 hours following drug administration. Blood samples were heparinized centrifuged and the plasma was separated and immediately stored at -20^{0}C until shipping to the analytical laboratory.

Assay Methodology:

Pharmacokinetic Results and Statistical Analyses:

Same as in Fasting Study Protocol above. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test; however, only T/R ratios of AUCs and CMAX were considered in determining the bioequivalency of the test product under non-fasting conditions.

Results:

Twent-three of twenty-four enrolled volunteers completed the clinical portion of the study. Subject # 5 withdrew voluntarily from the study after Period 1. Subject # 8 had no detectable acyclovir levels following dosing of the test formulation with fasting, and his AUC for the reference product with non-fasting was less than 12% of that of the next lowest subject (# 6). However, the statistical analysis was performed using both 23 and 22 (excluding # 8) data sets. The results summarized below were based on 23 data sets.

There was no significant difference (alpha=0.05) between treatments for CMAX and lnCMAX. There was a significant difference between treatments for AUC(0-T) (p=0.0016), AUC(0-Inf) (p=0.0109), lnAUC(0-T)(p=0.0086) and lnAUC(0-Infinity)(p=0.0135). The results are summarized in the tables below:

Table III
Acyclovir Comparative Pharmacokinetic Parameters
Dose = 400 mg; n = 23

Parameters	Apothecon's Mean (CV) Fasting	Apothecon's Mean (CV) Non-Fasting	Zovirax® Mean(CV) Non-Fasting	90% C.I.	Ratio T/R Non-Fasting
AUC (0-T) mcg.hr/ml	2.822*	4.027*	3.491*	[0.96;1.38]	1.15
AUC (0-Inf) mcg.hr/ml	3.188*	4.370*	3.894*	[0.95;1.33]	1.12
CMAX(mcg/ml)	0.6035*	0.7497*	0.6768*	[0.94;1.30]	1.11
TMAX (hrs)	1.70(41)	3.34(23)	2.55(31)		
KEL (1/hrs)	0.198(21)	0.221(23)	0.215(19)		
T1/2 (hrs)	3.66(22)	3.35(31)	3.35(22)		

*Geometric LS Means

Table IV

Comparative Mean Plasma Levels of Acyclovir

mcg/ml(CV)

Dose = 400 mg; n = 23

Hour	Apothecon's Fasting	Apothecon's Non-Fasting	Zovirax® Non-Fasting
0	0	0	0
0.25	0	0	0
0.5	0.169(58)	0	0.008(258)
1.0	0.543(43)	0.055(114)	0.199(82)
1.50	0.592(37)	0.224(61)	0.489(46)
2.0	0.588(37)	0.453(49)	0.679(32)
2.5	0.554(42)	0.611(40)	0.711(26)
3.0	0.504(47)	0.709(31)	0.677(24)
4.0	0.399(52)	0.685(27)	0.576(23)
5.0	0.290(48)	0.526(23)	0.438(21)
6.0	0.228(49)	0.411(24)	0.342(20)
8.0	0.149(44)	0.250(21)	0.212(20)
10.0	0.098(47)	0.153(18)	0.130(20)
12.0	0.058(69)	0.096(19)	0.087(18)
15.0	0.018(174)	0.039(87)	0.024(125)
19.0	0.006(324)	0.005(324)	0.005(324)
24.0	0.002(469)	0	0
AUC(0-T)mcg.hr/ml	3.258(43)	4.112(20)	3.967(18)
AUC(0-Inf)mcg.hr/ml	3.613(39)	4.423(18)	4.34(17)
CMAX	0.674(36)	0.781(28)	0.763(24)

Adverse Effects:

None of the adverse reactions reported was serious. There were two subjects who reported adverse effects during each test and reference treatments. The reactions judged probably or possibly related to the treatments were syncope and feeling "pins and needles" in left wrist (related to blood draw).

III. Dissolution Testing:

Drug (Generic Name): Acyclovir Capsules Firm: Apothecon
Dose Strength: 200 mg ANDA # 74-889
Submission Date: April 18, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXIII Basket X Paddle __ RPM __ No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 ml
Reference Drug: (Manuf.) Zovirax[R]; Burroughs-Wellcome
Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 9509B004 Strength (mg) 200			Reference Product Lot # 5M1295 Strength (mg) 200		
	Mean % Dissolved	Range	(S.D.)	Mean % Dissolved	Range	(S.D)
5	30.22		(17.3)	29.03		(8.67)
10	82.97		(9.90)	57.46		(15.3)
15	93.69		(3.30)	79.73		(14.6)
20	95.47		(4.72)	90.69		(7.60)
30	98.12		(4.09)	96.13		(2.94)
45	98.64		(2.64)	97.02		(2.55)
60	99.97		(2.44)	97.60		(2.82)

Firm's Specification:
NLT in 30min

IV. Comments:

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Apothecon on the test product, Acyclovir Capsules, 200 mg, lot # 9509B004, comparing it with the reference product, Zovirax[R] Capsules, 200 mg, lot # 5M1295, demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) under fasting and non-fasting conditions.

2. Food appeared to significantly increase AUCs (by approximately 40%), CMAX (by approximately 24%) and TMAX (by approximately 95%). This finding differs from that of Zovirax's manufacturer Burrough-Wellcome: "In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent."

V. Deficiency:

The dissolution testing for the test and reference products is not acceptable. The dissolution medium should be **water** instead of 0.1N H Cl, and the basket speed should be **100 rpm** instead of 50 rpm. The current FDA-recommended dissolution specification is NLT of LC dissolved in 30 minutes.

VI. Recommendations:

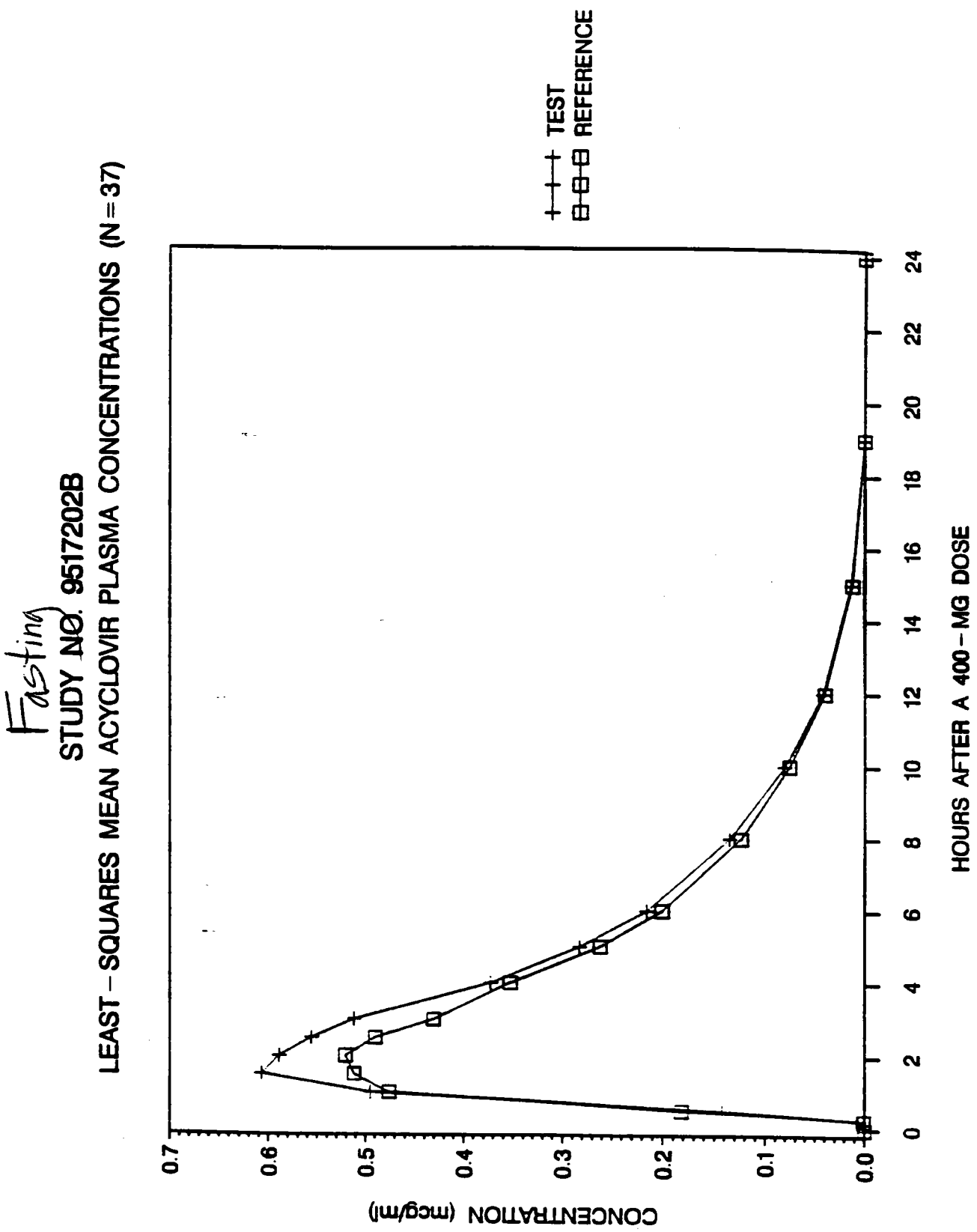
1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Apothecon on the test product, Acyclovir Capsules, 200 mg, lot # 9509B004, comparing it with the reference product, Zovirax[R] Capsules, 200 mg, lot # 5M1295, have been found **acceptable** by the Division of Bioequivalence. The studies demonstrate that the test product is bioequivalent to the reference product under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Apothecon on its Acyclovir Capsules, 200 mg, has been found **unacceptable** due to the reasons cited in the Deficiency above.

9-12-96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

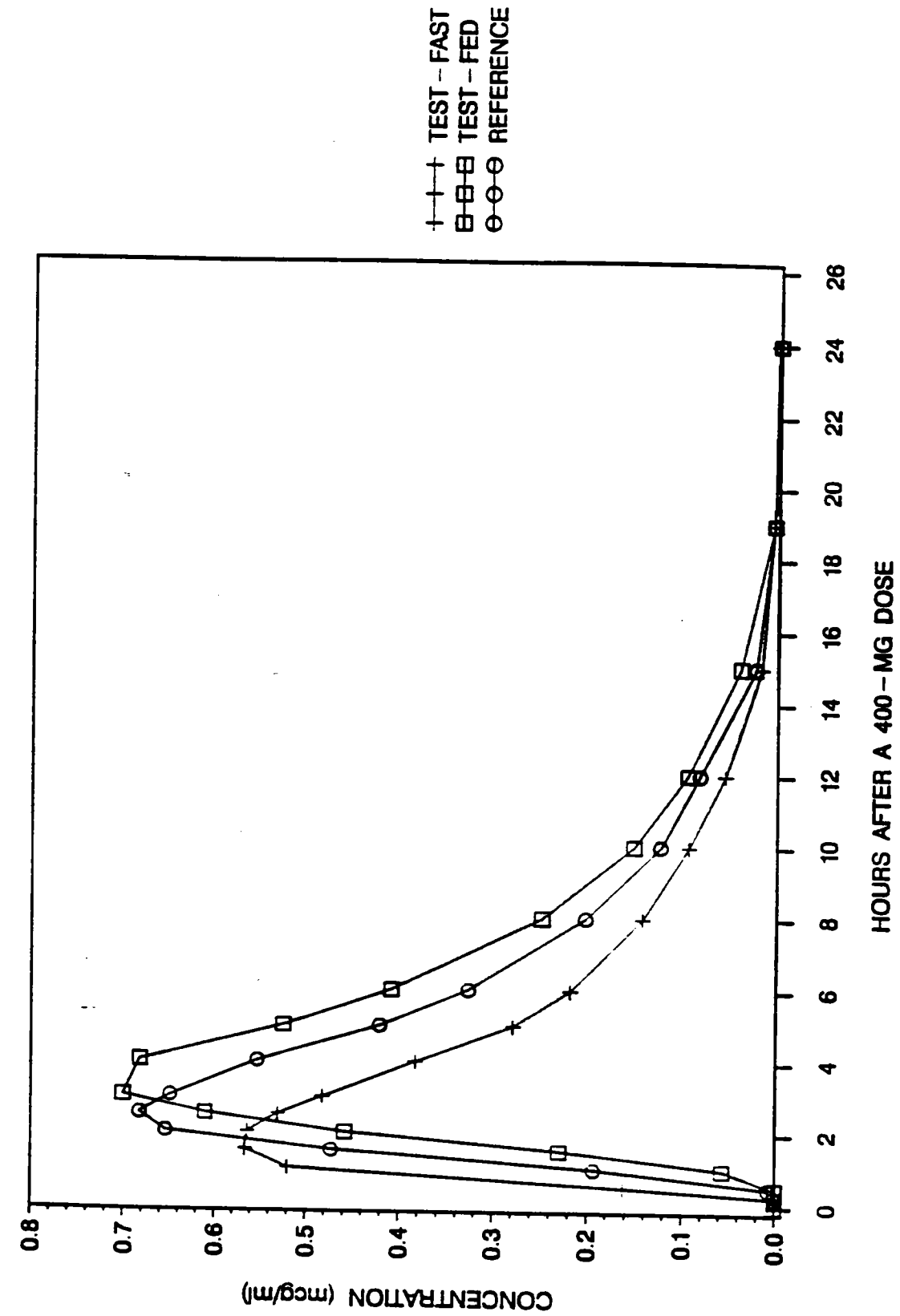
Wp # 74889 sd. 496 Attachment 1 of 3



NP # 74889 sd. 496 Attachment 2 of 3

Non-Fasting / Fasting

LEAST-SQUARES MEAN ACYCLOVIR PLASMA CONCENTRATIONS (N=23)
STUDY NO. 9517203B



WF #74889 sd 496 Attachment 3 of 3

VII. Components and Composition Statements

Composition

The composition information presented in this section accurately reflect the composition manufactured for bioequivalence and stability studies. Our proposed commercial batch size is capsules. A blank batch record for this batch size is included in Section "XI.A.5.".

The composition of the Acyclovir Capsules 200 mg formulation, the subject of this filing, is as follows:

Acyclovir Capsules

Ingredient	200 mg	Composition	Demonstration Tablet Batch Size*	Reason for Component
Compressed Capsule	(mg/cap)	%		
Acyclovir (Dry wt)	200.00	69.31		Active Ingredient
Sodium Starch Glycolate, NF				
Microcrystalline Cellulose, NF				
Povidone, USP				
Pregelatinized Starch, NF				
Magnesium Stearate, NF				
Capsule††				
Water Purified, USP†				
Total††	288.55	100.00		

* The demonstration batch size theoretically produces capsules of the 200 mg strength